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FOCUS

THEMATIC SECTION
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Multisite international collaborative clinical trials in mania

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Multi-regional collaborative clinical trials include those conducted across heterogeneous areas of the world under common protocols. Such trials appear to be driven primarily to provide data required for regulatory approval or licensing of new drug products in a relatively rapid and presumably efficient and cost-effective manner. Commonly, they include underserved populations and areas where costs of trials are lower than in most developed countries. In addition, such studies can potentially make innovative treatments widely and rapidly available in vast, international markets. Other potential benefits to collaborating sites may include diffusion of knowledge and improvement of research skills, as well as improvement of treatment and a broader salutary impact on health services and perhaps on employment opportunities and economic growth (Demol & Weihrauch, 1997; Glickman *et al*. 2009; Gopal *et al*. 2005; Greco & Diniz, 2008; ICH Guideline, 2002; Smulevich *et al*. 2005; U.S. FDA, 1998).

Successful conduct of international trials requires compliance with varying local and international laws, regulations and ethical requirements, and confronting a range of systems of review of ethical aspects of subject recruitment, compensation, consenting procedures, research protocols, and provision of aftercare – all which can add complexity. In addition, there is variance among regions, countries and cultures in levels of education, and in the nature of information, financial inducements, clinical care and aftercare provided to research subjects. Complexities arise also from culture-dependent conceptualizations of mental disorders, criteria for diagnosis, and efforts at validating, interpreting and scoring of symptom ratings designed to characterize changes during treatment, and methods for detecting adverse events. In the continuing quest to define core or universal features of psychiatric disorders, it is crucial to consider the anthropological and cultural context in which they develop and are modified (Karno & Jenkins, 1993; Lopez-Ibor, 2003; Westermeyer & Janca, 1997), particularly without biological markers or other reliable standards by which to verify diagnoses (Robins, 1985). All of these variables, ideally, need to be managed so as to support pooling of trials' data across sites (Glickman *et al*. 2009; Ibia *et al*. 2010; Saillot & Paxton, 2009). Clinical, cultural, social and economic variance among sites is likely to have a greater impact on trials in psychiatric than general medical disorders, owing to heavy reliance on observation and scoring of subjective experience in mental illnesses. Although such concerns are plausible, there has been remarkably little research to test comparability across culturally dissimilar trial sites (Tamayo *et al*. 2007; Vieta *et al*. 2011; Yildiz *et al.* 2011*a*, *b*). The suspected high risk of variance in the conduct and findings from particular sites in large, international collaborative trials, itself, raises important questions. A new retrospective analysis of a controlled trial of ziprasidone in mania by Vieta and his colleagues (2011) indicates major national differences in patient characteristics, body-weight-corrected daily drug doses (mg/kg), and in findings regarding efficacy and adverse effects associated with the test drug, an active comparator, and

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Focus on: Vieta *et al.* (2011). Impact of geographical and cultural factors on clinical trials in acute mania: lessons from a ziprasidone and haloperidol placebo-controlled study.

Table 1. Factors that can complicate interpretation of multisite, international collaborative treatment trials

- Variance in the nature and severity of illnesses encountered among subjects and in their prior responses to treatment
- Largely untested variance in regional, national, and cultural conceptions of disorders
- Largely untested local variance in clinical diagnostic criteria and their impact on case identification
- Largely untested variance in local interpretation (by patients and raters) and scoring of items on standard symptom rating scales developed in other cultures
- Variance in reporting adverse events by patients and raters
- Inadequate statistical power to test fairly for site-variance, leading to false-negative inferences
- Inferring universal effects by pooling data, despite major differences among sites
- Loss of statistical power and increased cost as site counts increase, owing to increased placebo effects; lack of statistical power to detect site variance owing to small numbers of subjects/site
- Regulatory, marketing, and ethical challenges arising from excessive reliance on pooled, average results despite major apparent differences in efficacy or safety among sites
- Potential ethical concerns about financial and clinical inducements provided to potential subjects, including the nature of their aftercare following an experimental trial, as well as arising from site-variance in the ethical review and consenting processes
- Potential ethical concerns about exposing more patients than necessary to placebo or inactive treatments
- Limited motivation to learn from research on site variance as a means of improving trial design and efficiency, as well as to identify characteristics of subgroups who may respond especially well or poorly to a new treatment

a placebo control. Notably, in the USA, antimanic responses were modest and similar for ziprasidone and haloperidol, against a relatively large placebo-associated effect, and with relatively frequent reporting of adverse events. In contrast, in India and Russia, reported placebo responses were much lower, drug responses greater, haloperidol was more effective than ziprasidone, and adverse event reports were fewer (Vieta *et al*. 2011). It is likely that similar variance among sites would be found in many large, international trials if such information were reported (Tamayo *et al*. 2007).

Reasons for limited drug–placebo contrasts in the USA compared to other countries may reflect recent secular trends towards declining response rates in trials (Keck *et al*. 2003; Kemp *et al*. 2010). In turn, this trend may reflect a tendency for potential research subjects found in academic or speciality clinics as well as in practices accessed by many contract research organizations, to include a relatively high proportion of patients already showing limited responses to standard treatments and eager to try new options, or patients whose illnesses are not severe and may respond to placebo. Such tendencies can encourage searches for more severely ill or less extensively treated patients for international trials.

Recent meta-analytical reviews of studies of antimanic agents found to be effective, included 48 controlled trials, mostly large international collaborations involving of 35.8 ± 18.2 sites/trial, 94% (45/48) of which were supported by manufacturers of tested products (Yildiz *et al*. 2011*a*). Subjects/site averaged 6.8 ± 5.6 in trials involving more than one site, suggesting a high risk of uncontrolled variance in methods and outcomes among sites with so few subjects, as well as such low statistical power that site variance may escape detection. None of these trial reports provided evidence that diagnostic or assessment methods, usually standardized elsewhere, tested for reliability or validity in local populations, or shown to be comparable across sites, nor were site-specific results considered individually before pooling of data to determine overall, average, effects. This observation makes the rare *post-hoc* re-analysis by Vieta *et al*. (2011) all the more striking. Lack of information about basic questions pertaining to international collaborative trials severely limits conclusions that can fairly be drawn about them, notwithstanding the importance of such information in establishing the scientific validity of the methods involved and broad generalizability of findings (Anello *et al*. 2005; Jones *et al*. 1998). Moreover, the likelihood of obtaining data pertaining to variance among sites or nations is limited by the apparent primary aim of seeking pooled results with large numbers of subjects to provide great statistical power for average findings, to support regulatory approval.

Despite the constraints imposed by the rarity of reported site-specific findings from most international collaborative trials (at least for acute mania), some considerations require further attention. One is whether pooled findings can be taken as

representative of all participating sites. The findings of major national differences in patient characteristics, placebo responses, drug effects, and adverse-event reports by Vieta *et al*. (2011) strongly suggest that pooling can yield results that may not apply to all sites and cultures. The option of including more patients per site to provide sufficient statistical power to test quantitatively for local effects is likely to prove very expensive and logistically cumbersome (Uesaka, 2009). Moreover, there would be little current motivation to address site variance if the topic were considered largely of academic interest. However, potential regulatory, commercial, and even ethical aspects of the situation may encourage greater access to information about site variance, perhaps as a regulatory requirement or as a consideration by editors of journals publishing reports of such trials. For example, one can question whether pooled data can fairly support licensing and marketing of a new drug in a collaborating region or country where local findings are at variance with overall pooled outcomes in international trials. In turn, there may be ethical questions about the appropriateness of marketing a new drug in a region or country where the research support for claims of local efficacy and safety can be questioned. We also agree with Vieta *et al*. (2011) that progress in experimental therapeutics in psychiatry can be enhanced by routine consideration of differences among patient subgroups in beneficial or adverse responses to experimental treatments. Such refinements may also enhance efforts to target new treatments at particular clinical subgroups, with potential support for data-based marketing efforts.

Another practical consideration arises concerning multisite, collaborative trials seeking data on the efficacy and safety of new drugs relatively rapidly, efficiently, and cost-effectively. Recent analyses of all available controlled trials in mania (Yildiz *et al.* 2011*b*) indicated, paradoxically, that larger numbers of sites and subjects can actually *reduce* drug–placebo contrasts. Study size had little effect on drug-associated responses, but led to relatively greater placebo responses and lower drug–placebo contrasts (apparent efficacy). This effect may arise from methodological variance among heterogeneous sites to increase random responses ('noise') during treatment with a placebo, with regression to mean response assessments that are greater than have been found in smaller, and presumably less heterogeneous and better-controlled, trials (Pope *et al*. 1991; Yildiz *et al.* 2008, 2011*b*; Zarate *et al*. 2007). Implications of this finding may include a paradoxical *loss* of statistical power and *less* favourable cost-benefit relationships in very large, heterogeneous trials. A further ethical concern, particularly when a placebo or ineffective treatment is included in the trial design, is that more patients would be put at risk of ineffective treatments than may be scientifically necessary or clinically desirable.

The Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (U.S. FDA, 1998) and International Guideline for Clinical Requirements for Registration of Pharmaceuticals for Human Use (ICH Guideline, 2002) identify characteristics aimed at strengthening the level of evidence provided by large, international, collaborative treatment trials. Important among these are that no single study-site should provide such a large proportion of patients as to risk a disproportionate favourable or unfavourable impact on pooled findings (Anello *et al*. 2005); estimated effects should be consistent across sites and investigators (Demol & Weihrauch, 1997); and multiple outcome measures should yield consistent findings (Glickman *et al*. 2009). Considerations discussed above are summarized in Table 1.

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Statement of Interest

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